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Tissue Segmentation in Acute Ischemic Stroke

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Abstract

One guideline recommended method to help clinicians triage acute ischemic stroke patients for mechanical thrombectomy (MT) is based on the estimation of infarct and mismatch volume as estimated by CT Perfusion (CTP). However, prior studies had shown that the quantitative accuracy of CTP perfusion maps varies with the software (numerical algorithm) used which, by inference, means that thresholds for infarct and mismatch volume estimation could be software dependent. Clinically, thresholds of the RAPID software (iSchemiaView, Inc.) had been validated in the DEFUSE 3 trial. The goal of this study is to compare CT Perfusion 4D (CTP4D, GE Healthcare) thresholds to those of the RAPID software in a clinical evaluation.

Using clinical CTP studies from the ISLES database*, it was shown that when using CTP4D thresholds of rCBF (ischemic to normal CBF ratio) < 10% and TMax >7s thresholds, CTP4D derived infarct and mismatch volumes closely matched those from RAPID and the estimated infarct volumes from CT Perfusion were significantly correlated ($P < 0.01$) to those measured using the clinical gold standard of MR DWI, with correlation coefficient of 0.84 and 0.87 for RAPID and CTP4D respectively. Moreover, MT recommendation based on the two software using the calibrated equivalent thresholds agreed at the individual patient level to a high degree - 97% and 3% concordance and discordance rate, respectively.

Introduction

Stroke is the second leading cause of death, and third leading cause of disability worldwide according to the World Health Organization[1]. Since the seminal IV tissue plasminogen activator study demonstrating effectiveness to limit neurological sequelae for acute ischemic stoke in 1995[2], treatment has been expanded to include mechanical thrombectomy (MT). The availability of treatment options has spurred the development of acute stroke imaging, particularly using CT, to help triage patient into appropriate treatment. CT Perfusion (CTP) is a minimally invasive imaging technique that produces quantitative maps of cerebral blood flow, cerebral blood volume, mean transit time and other hemodynamic parameters, which are useful for assessing tissue viability[3,4]. Because of its 24-7 accessibility, CT could help improve stroke care by assisting the clinicians in the selection of the optimal treatment for individual patients. For example, the five (ESCAPE, EXTEND-IA, MR CLEAN, REVASCAT and SWIFT-PRIME[5-9]) successful trials of treating large vessel occlusion within 6 to 12 hours of symptom onset with MT had higher rates of good functional outcome in the MT group. Of these trials, CTP was one of the crucial MT selection criterion in the EXTEND-IA trial. The utility of CTP as one of the additional selection criteria to select patients for MT was further confirmed by DEFUSE 3[10] which extended the treatment time window to 16 hours. DEFUSE 3 used thresholds applied to CTP derived CBF and Tmax maps to estimate infarct core and penumbral volume. Patients were eligible for treatment if penumbra volume was 1.8 times larger than the infarct, infarct volume was < 70mL, and penumbra volume was > 15mL[10].

The goal of the current study was to compare the results obtained from thresholded CBF and Tmax maps derived by the RAPID and CT Perfusion 4D software (iSchemiaView, Inc. and GE Healthcare respectively), as well as investigate whether these results would trigger the same treatment decision using the DEFUSE 3 criteria.

*(http://www.isles-challenge.org/)

Materials and methods

The evaluation was performed on the set of patients used in the Ischemic Stroke Lesion Segmentation (ISLES) 2018 Challenge organized by the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI) to test competing software in segmenting stroke lesions based on acute CT Perfusion imaging*. The 2018 Challenge database had 103 patients each had an admission CTP study followed by a MR DWI study within a 3-h time window. Patients were not treated in the interval time between CTP and MR study. This study used a subset of 63 out of the 103 stroke patients for whom CT Perfusion maps generated by the RAPID software and manual segmentation of the DWI lesion were available in the ISLES 2018 database.

Perfusion Map Generation with CTP4D

CTP studies were processed with CTP4D (Version Ver16.0-2.216) Stroke protocol where the arterial input and venous output time density curve (TDC) were automatically generated by the software from a major artery (e.g. internal carotid, middle and anterior cerebral artery or others) and a major draining vein (e.g. posterior superior sagittal sinus, transverse sinus or others) respectively and manually corrected if necessary. The CTP source dynamic images were then smoothed with an edge preserving bilateral filter. After smoothing, CT Perfusion maps were calculated by deconvolving the arterial from the brain time-density curves based on the Johnson-Wilson-Lee (JWL) model[11] to obtain the flow scaled impulse residue function (RF) from which blood flow, blood volume, mean transit time and Tmax were determined[11].

Processing of ISLES Patient Studies and Comparison of Infarct and Mismatch Volume

The ISLES CTP studies were processed with the CTP4D software (Ver16.0-2.216) to generate CBF and Tmax maps. On the other hand, RAPID CBF and Tmax maps were downloaded from ISLES 2018 website*. Within the RAPID software, infarct volume is defined by rCBF< 30%, and mismatch volume by Tmax > 6 s and rCBF > 30%[9,15]. Within the CTP4D software, the rCBF threshold is set to rCBF<10%, and mismatch volume by Tmax > 7 s and rCBF >10%. The difference of thresholds between RAPID and CTP4D is explained by the differences in the two software models and algorithms: CTP4D uses the JWL model[11] while RAPID uses model-independent Wiener filtering[12] to calculate the flow scaled impulse residue function by deconvolving the arterial time density curve from the brain tissue time density curves (TDC). As a consequence, RAPID thresholds cannot be used directly with CTP4D for infarct or mismatch volume estimations. Each deconvolution method can lead to a different level of bias in the estimated cerebral blood flow (CBF) and hence relative CBF (rCBF, ischemic relative to contralateral hemispheric CBF)[13,14] which is used in the current clinical paradigm (DEFUSE 3 criteria[10]) of measuring infarct volume from acute CTP studies.

Based on prior simulation studies with a digital perfusion phantom, we found that a 10% CTP4D rCBF is equivalent to a 30% RAPID rCBF[15]. To validate this correspondence in rCBF threshold, the predicted infarct volumes by RAPID and CTP4D were compared against that from the follow-up MR DWI using correlation and Bland-Altman analysis[15].

The performance of RAPID and CTP4D was also compared in the triage of ISLES patients for MT using the DEFUSE 3 criteria[10]: infarct volume < 70 mL, ratio of perfusion deficit to infarct volume > 1.8 and mismatch volume > 15 mL. The number of concordant and discordant cases with respect to MT triage were reported.

Statistical Analysis

All quantitative values were quoted as median (interquartile range). Comparison of quantitative values were performed with correlation, linear regression and/or Bland-Altman analysis[16].

Results

Characteristics of ISLES Patients and their Ischemic Lesion

The 63 patients from the ISLES database were imaged first with CTP and then had MR DWI within 3 hours of CTP imaging (range 15-181 mins). Both imaging studies were performed before any treatment. About 50% of the CTP studies were acquired as two separate 4 cm slabs with two contrast injections. Slabs were processed separately but the infarct and mismatch volumes of each slab were summed together in the following analysis.

Mean DWI infarct volume was 47.6 mL (IQR: 13.8 – 60.9 mL). Based on RAPID maps, the median rCBF < 30% (infarct) volume was 18.4 mL (IQR: 2.8 – 21.0 mL) and the median Tmax > 6s (mismatch) volume was 68.7 mL (IQR: 35.6 – 83.2 mL). From CTP4D maps, the median rCBF < 10% (infarct) volume was 18.2 mL (IQR: 3.9 – 22.9 mL) and the median Tmax > 7s (mismatch) volume was 76.9 mL (IQR: 38.4 – 105.6 mL).

Comparison of Infarct and Mismatch Volume Estimated by RAPID and CTP4D in ISLES Patients

Infarct volume was segmented from RAPID and CTP4D CBF map using an rCBF threshold of 30%[10,17] and 10% respectively. These estimated infarct volumes from CTP were significantly correlated ($P < 0.01$) to those measured using the clinical gold standard of MR DWI, Figure 1 (A) & (B), with correlation coefficient of 0.84 and 0.87 for RAPID and CTP4D respectively.

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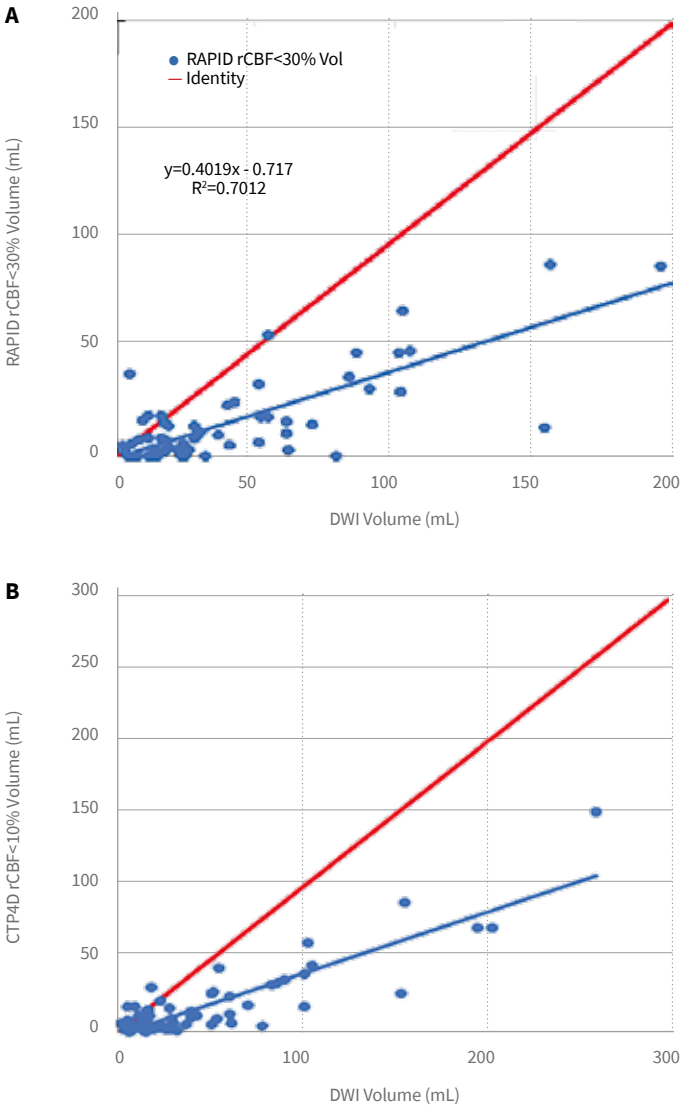

Figure 1. Correlation of RAPID (A) and CTP4D (B) estimated infarcted volumes with rCBF threshold of 30% and 10% respectively to those measured with MR DWI. The regression line is shown in blue while the identity line in red.

Figure 2 (A) & (B) show the Bland-Altman analysis of RAPID (rCBF < 30%) and CTP4D (rCBF < 10%) derived infarct volumes versus those from MR DWI[16]. The difference between MR DWI and RAPID or CTP4D volumes was adjusted for linear dependence on the average volume as suggested by Bland-Altman16. The mean adjusted difference between RAPID and MR DWI infarct volumes was 0.0mL (limits of agreement of 76 mL) while that for CTP4D was 0.0mL (limits of agreement 68.6 mL). The almost complete overlap of the limits of agreement suggests that RAPID and CTP4D are equivalent in estimating infarct volumes relative to MR DWI.

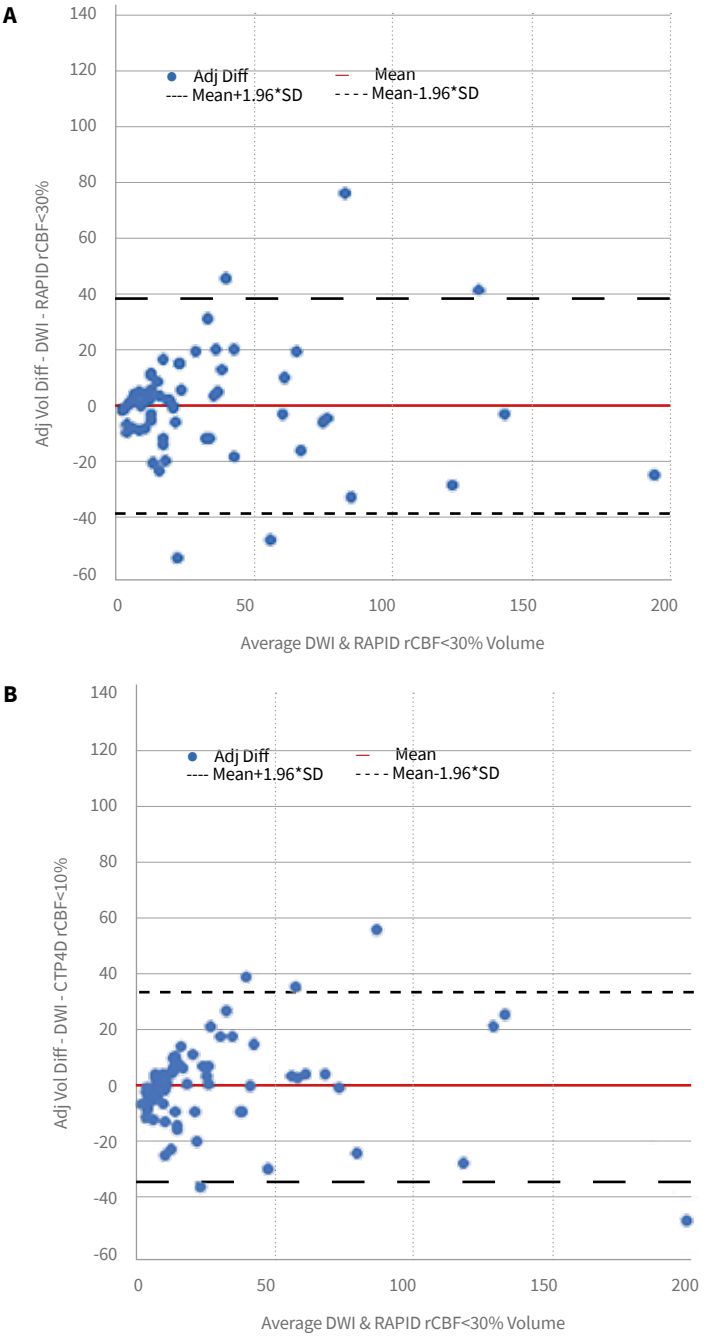

Figure 2. Bland-Altman analysis of (A) RAPID infarct volume (rCBF <30%) and (B) CTP4D infarct volume (rCBF < 10%) versus MR DWI infarct volume. All volumes in units of mL.

Figure 3 shows that the CTP4D mismatch volume (Tmax > 7s & rCBF>10%) was significantly correlated to the RAPID volume (Tmax > 6s & rCBF>30%) at P < 0.01.

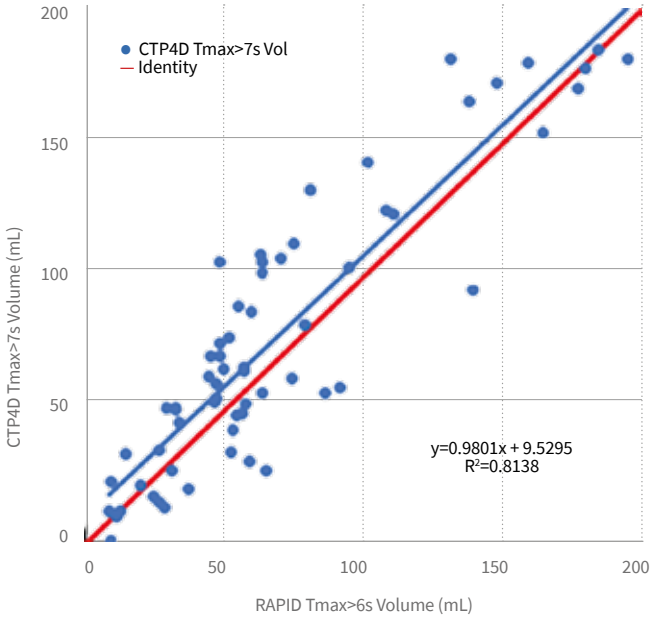

Figure 3. Correlation of CTP4D mismatch volume with that of RAPID.

Comparison of MT Decision Using RAPID and CTP4D Perfusion Maps

In the absence of a gold standard to assess the relative performance of the two software for the estimation of mismatch volume based on Tmax threshold, a clinically relevant combined evaluation of the infarct and mismatch volumes is to use them for a simulated MT triage among the ISLES patients based on the DEFUSE 3 criteria[10]. Table 1 shows the concordant and discordant rate of the MT triage between RAPID and CTP4D were 97% (61/63) and 3% (2/63) respectively.

		CTP4D	
		Y	N
RAPID	Y	54	1
	N	1	7

Table 1. 2 x 2 contingency table of concordance and discordance in thrombectomy decision based on DEFUSE 3 criteria applied to CTP4D and RAPID CBF and Tmax maps.

Discussion

One guideline recommended method to triage acute ischemic stroke patients for MT is based on the estimation of infarct and mismatch volume as estimated by CTP[18]. However, Kudo *et al*[13,14] had shown that the quantitative accuracy of CTP perfusion maps varies with the software (numerical algorithm) used which, by inference, means that thresholds for infarct and mismatch volume estimation could be software dependent. Clinically, thresholds of the RAPID software (iSchemiaView, Inc.) had been validated

in the DEFUSE 3 trial. The goal of this study was to compare the thresholds used in CTP4D to the ones used in RAPID.

For this purpose, we compared infarct volumes estimated from CTP4D derived CBF maps using the rCBF threshold of 10% with those delineated in follow-up MR DWI images using regression and Bland-Altman analysis (Figure 1(B) & Figure 2(B)). Figures 1(A) & 2(A) show the same comparisons carried out with RAPID CBF maps with a rCBF threshold of 30%. Both regression and Bland-Altman analysis show that the infarct volumes estimated by both RAPID and CTP4D were correlated to the MR DWI delineated infarct volume in the same way. Additionally, differences between the infarct volumes estimated by RAPID and CTP4D were not significant ($P > 0.5$, Student's t-test of paired samples).

Concerning mismatch volumes delineated with Tmax threshold of 6s and 7s respectively from RAPID and CTP4D Tmax maps, again they were significantly correlated ($R= 0.90$; $P < 0.01$) with a regression slop of 0.98, as well there were not significant differences between the two volumes ($P > 0.3$, Student's t-test).

Finally, the rCBF and Tmax thresholds for RAPID and CTP4D were applied to respective CBF and Tmax maps to determine the agreement between the two software in assisting the clinicians in recommending ISLES patients for MT. This resulted in a concordance and discordance rate of 97% and 3% respectively.

Tissue status, infarct or penumbra (mismatch) has a multifactorial dependence and may not depend solely on a single CBF and Tmax threshold19,20. The dependence of these thresholds on other relevant parameters including onset to imaging time[21] requires further investigation which is outside the scope of the present study.

Conclusion

In summary, the clinical ISLES CTP study results suggest that CT Perfusion 4D derived infarct and mismatch volumes closely match those from RAPID and assisting clinicians with the mechanical thrombectomy recommendation based on the two software has a high concordance rate at the individual patient level. However, use of calibrated equivalent thresholds obtained is required. As well, all tissue segmentation should be interpreted in light of all available imaging and clinical data to prevent errors as discussed in the literature[19-22].

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